SUMMARY MINUTES

OF THE

OBSTETRICS AND GYNECOLOGY DEVICES

ADVISORY PANEL MEETING

SIXTY-FIFTH MEETING

OPEN SESSION

April 22, 2002

Gaithersburg Marriott
Gaithersburg, Maryland

Obstetrics and Gynecology Devices Panel
April 22, 2002
Gaithersburg Marriott

Roster

Jorge D. Blanco, M.D., Chair
Regional Perinatal Center
Odessa Regional Hospital
Odessa, TX

Carol L. Brown, M.D.
Weill-Cornell Medical College
Memorial Sloan-Kettering Cancer Center
New York, NY

Gary S. Eglinton, M.D.
Department of Obstetrics and Gynecology
New York Hospital Medical Center of Queens
Flushing, NY

Jay D. Iams, M.D.
Department of Obstetrics and Gynecology
Ohio State University
Columbus, OH

Kleia R. Luckner, J.D., M.S.N.
(Consumer Representative)
Women's Ambulatory Health
The Toledo Hospital
Toledo, OH

Mary Lou Mooney, R.A.C.
(Industry Representative)
Seno RX, Inc.
Aliso Viejo, CA

Michael Neuman, M.D., Ph.D.
Joint Program of Biomedical Engineering
University of Memphis
Memphis, TN
Mary Jo O'Sullivan, M.D.
Department of Obstetrics & Gynecology
University of Miami/Jackson Memorial Hospital, Hoetz Center
Miami, FL

Susan M. Ramin, M.D.
Department of Obstetrics and Gynecology and Reproductive Sciences
University of Texas—Houston Medical School
Houston, TX

Richard E. Ringel, M.D.
Pediatric Cardiology
Johns Hopkins Hospital
Baltimore, MD

David B. Seifer, M.D.
Division of Reproductive Endocrinology & Infertility
University of Medicine & Dentistry of New Jersey
New Brunswick, NJ

Nancy C. Sharts-Hopko, Ph.D.
College of Nursing
Villanova University
Villanova, PA

Alicia Y. Toledano, Sc.D.
Center for Statistical Sciences
Brown University
Providence, RI

Robert N. Wolfson, M.D., Ph.D.
Specialists in Women's Health
Colorado Springs, CO

FDA Representatives

Joyce Whang, Ph.D.
Panel Executive Secretary

Nancy C. Brogdon
Director, Division of Reproductive, Abdominal, and Radiological Devices

Colin Pollard
Chief, Obstetrics and Gynecology Devices Branch

Julia Corrado, M.D.
Medical Officer, Obstetrics and Gynecology Devices Branch

Kathryn S. Daws-Kopp
Electrical Engineer/Lead Reviewer

Sponsor Representatives

Karl G. Rosen, M.D., Ph.D.
Karel Marsal, M.D., Ph.D.
Ingemar Kjellmar, M.D.
Lawrence D. Devoe, M.D.

OPEN SESSION—APRIL 22, 2002

Panel Chair Jorge D. Blanco called the Open Session to order at 8:05 a.m., asking panel members to introduce themselves and state their areas of expertise. **Panel Executive Secretary Joyce Whang, Ph.D.**, listed two tentative advisory panel meeting dates of July 22-23 and October 21-22, 2002. Dr. Whang read appointments to temporary voting status for Gary S. Eglinton, M.D., Jay D. Iams, M.D., Michael Neuman, M.D., Ph.D., Susan M. Ramin, M.D., Richard E. Ringel, M.D., and Robert N. Wolfson, M.D., Ph.D. Dr. Whang also read the conflict of interest statement. She noted that the FDA had granted a waiver to Richard E. Ringel for his stockholdings in a competing firm and that his full participation would be allowed. The Agency had also considered matters concerning Gary S. Eglinton, Michael Neuman, and Robert N. Wolfson and had allowed their full participation.

Introductory Remarks

Colin Pollard, Chief of the Obstetrics and Gynecology Devices Branch, reviewed Branch activities since January 2001. He stated that two premarket approval applications (PMAs) had been approved: the NovaSure endometrial ablation system in September 2001 and Lea's Shield in March 2002. He added that the Office of Postmarketing Surveillance would be giving a presentation on postmarketing studies at the upcoming July panel meeting.

Mr. Powell introduced the subject for panel discussion, PMA P020001 for the Neoventa STAN S21 Fetal Heart Monitor. He stated that while most electronic fetal monitors are class II devices subject to 510k approval, the STAN 21 has new features such as the use of

a fetal ECG analysis with standard fetal heart rate and ST waveform analysis to improve assessment of fetal health. Mr. Powell read the proposed intended use, reviewed the regulatory framework for PMA reviews and the panel's options for vote recommendations, and outlined the day's agenda.

Open Public Hearing

Panel Chair Dr. Blanco invited comments from the public, recognizing Raul Artal, M.D., vice chair of the American College of Obstetricians and Gynecologists (ACOG) Committee on Obstetric Practice. Dr. Artal stated that the ACOG Committee had reviewed the summary of safety and effectiveness data on the Neoventa device, the publications listed in the summary, and a detailed published analysis of the Swedish randomized controlled trial of the STAN device. The recommendation of the ACOG Committee on Obstetric Practice was that although this new technology appeared very promising, the Committee could not endorse the adoption of this device in clinical practice. He added that ACOG is particularly concerned with introduction of new technology to clinical practice that could further escalate the cost of medical care without necessarily improving clinical outcome. The ACOG Committee urged the panel to clarify five issues with the sponsors, including false positive and false negative results for detecting metabolic acidosis/hypoxia, influence of other events on ST waveforms in the fetus, protocol violations, sensitivity and specificity of cardiotocography (CRT)+ST for detecting fetal metabolic acidosis/hypoxia, and the likelihood ratio.

There were no other requests to address the panel.

Sponsor Presentation

Karl G. Rosen, M.D., Ph.D., gave an overview of the STAN concept as a method of intrapartum fetal monitoring to identify fetuses at risk of an adverse outcome. He reviewed the tools of fetal surveillance for blood-based assessment or through specific organ or tissue functions such as metabolic acidosis, ST analysis, or fetal heart rate. Dr. Rosen discussed observations made during sheep studies on hemodynamic, cerebral, and metabolic functions during labor, fetal myocardial metabolism and ST changes, and regulatory mechanisms, showing normal ST waveforms, ST waveforms with hypoxia, and biphasic ST waveforms. Clinical research and development included a randomized controlled trial (RCT) in Plymouth, England, an observational multicenter study in the European Union (EU), a Nordic observational multicenter study, a Swedish RCT, and a EU project on clinical implementation.

Dr. Rosen presented the published results of the Plymouth RCT, which compared use of the STAN device with use of fetal heart rate monitoring alone, and the Nordic study. The Plymouth trial showed a need to refine the technology by digital signal processing and automatic ST analysis, but also supported the premise that an ST rise shows a fetus responding to hypoxia and a biphasic ST pattern shows a fetus not fully capable of responding or not having had time to respond yet. Dr. Rosen also explained the STAN simplified clinical guidelines for intervention. Data from the Nordic observation study of 573 cases also showed a greater positive predictive value for CTG +ST changes at different cut-offs of cord artery pH than for CTG changes alone.

Dr. Rosen then described the main objectives and study design of the Swedish RCT, a multicenter study of 4966 labors comparing CTG+ST analysis to CTG alone that sought to

reduce the number of newborns with cord artery metabolic acidosis by at least 50% and to reduce operative delivery rate for fetal distress without increasing the total rate of operative deliveries. He outlined inclusion and exclusion criteria and clinical management guidelines for control and device group. An interim analysis after 1800 cases showed deviations from these guidelines with six babies exposed to unnecessary oxygen deficiency, which led to repeated training and continuing case discussions. Dr. Rosen described the characteristics of the 2519 STAN group and the 2447 control deliveries, noting 574 exclusions for inadequate recordings for various reasons. The overall outcome showed a 54% reduction in metabolic acidosis and a 19% reduction in operative delivery for fetal distress (ODFD) before retraining and a 67% reduction in metabolic acidosis and 38% reduction in ODFD after retraining. Rates of moderate or severe neonatal encephalopathy in newborns were much lower for the STAN group than for control (.40 compared to 3.3 per 1000), as were rates of ODFD and metabolic acidosis.

Dr. Rosen also presented data on 16 months of experience with the STAN device as a part of routine obstetric care in the city of Gothenburg in terms of ODFD rates and metabolic acidosis.

Ingemar Kjellmar, M.D., discussed perinatal care in Sweden, presenting statistics on births per year, perinatal mortality, and national guidelines for resuscitation since 1972. He looked at cerebral palsy rates in Western Sweden from 1954 through 1994, with follow-up into young adulthood of infants with perinatal asphyxia. He concluded that the prognosis is generally excellent for resuscitated babies, although those who develop severe hypoxic ischemic encephalopathy (HIE) have a grim prognosis.

Karel Marsal, M.D., Ph.D., discussed management of labor and delivery in the United States and Sweden. He noted the greater use of midwives for uncomplicated labor and delivery in Sweden, but a comparison of the U.S. and Swedish national guidelines showed labor and delivery management to be similar. He thought there was a somewhat more liberal use of electronic fetal monitoring in normal pregnancies in Sweden than in the United States, but said this observation was not proven scientifically.

Lawrence D. Devoe, M.D. discussed applicability and usability of the STAN device in the United States. He summarized the history of EFM, beginning with the nonrandomized controlled observations made in the early EFM trials, which presented a sanguine outlook for EFM use. A 2001 meta-analysis comparing EFM combined with FBS to auscultation in 13 RCTs, however, showed more Cesarean sections (C-sections) and operative deliveries in the EFM group, a similar perinatal death rate, and fewer neonatal seizures only in the EFM and FBS sample.

Dr. Devoe also listed current issues about EFM, such as observer reliability and reproducibility, FHR interpretation and clinical correlates, and use of ancillary assessment methods. He summarized the problems involved in each of these issues and the current state of knowledge from ongoing studies. Dr. Devoe called attention to the ACOG technical bulletins on evaluation and management of nonreassuring FHR patterns, noting that the current status places the clinician in a dilemma with limited supportive data to determine the best management, resulting in a probable excess of risky obstetric interventions without demonstrable benefit. He cited conclusions from a National Institutes of Health workshop on the need for an evidence-

based algorithm for handling questionable FHR tracings that are neither normal nor clearly predictive of fetal asphyxia.

Dr. Devoe offered ideas on what EFM should look like in the 21st century, using a range of new technologies such as Doppler, fetal oximetry, or ECG waveform analysis. After reviewing the current knowledge about and limitations of each technology, Dr. Devoe looked at possible targets for fetal intervention. He suggested that elimination of HIE/cerebral palsy was unrealistic, given the infrequency of the event and the size of the sample needed. Two other targets, reduction in profound acidemia/asphyxia and avoidance of unnecessary intervention, he saw as having been achieved in the Swedish RCT under discussion. He concluded that the Stan S21 system had been shown to address both these targets and that the scientific foundation for the higher level FECG analysis had been established in the laboratory and clinical setting.

FDA Presentation

Kathryn S. Daws-Kopp, lead FDA reviewer, acknowledged the FDA review team members and summarized the history of the FDA review of the STAN 21 device. After sponsor briefings on the Plymouth and Swedish RCTs in 1999, a PMA modular review began, with the general information module resolved and other modules rolled into the current PMA review. Ms. Daws-Kopp reviewed the device design in terms of components and mechanism of action. She described the areas reviewed such as software, hardware, biocompatibility, bioresearch monitoring, manufacturing compliance, and clinical and statistical analysis. Ongoing engineering issues included signal quality, validation testing of standard components, bioresearch monitoring, and manufacturing.

Julia Corrado, M.D., gave the FDA clinical review. After reading the proposed indication for use, she explained that the FDA clinical review placed primary emphasis on the Swedish RCT and clinical issues arising from it, along with a summary of other clinical experiences with the STAN device in EC countries. These studies included the Plymouth RCT, the EC multicenter trial, the Nordic observational multicenter trial, the Swedish RCT, and data from the city of Gothenburg. Of these, the EC multicenter program, which established centers of excellence in 10 countries for training and knowledge dissemination, was ongoing and had, with the other studies, produced a large body of clinical data. However, only the Swedish RCT was a prospective, randomized, multicenter, controlled study.

Dr. Corrado explained the Swedish study objectives and endpoints (metabolic acidosis, neonatal morbidity, and frequency of operative delivery). On safety, she stated that there were no new safety issues involving the components of the device because they are already in wide use. Safety implications of the data interpretation and resulting management decisions, however, are still part of the FDA review.

Efficacy was based on an intent-to-treat analysis and a second analysis on adequate recordings. The first analysis, intent to treat, was based on 4966 patients, of whom 360 STAN patients and 368 control patients were eliminated because the cord blood sample was inadequate. Of the remaining patients, the STAN group had a statistically significant reduction in metabolic acidosis and in operative delivery for fetal distress as compared to the control group, although the rate of C-section for fetal distress was not significantly lower than the control.

The second analysis was made on the basis of adequate recordings, with some 1926 STAN patients and 1871 control patients. Reasons for inadequate recordings were congenital

malformations, insufficient time on the STAN monitor, too much time between removal of the device and delivery, and other. In this analysis, the STAN group showed a statistically significant improvement in metabolic acidosis, in operative delivery for fetal distress, and in C-section for fetal distress, as compared to the control group. Dr. Corrado explained that the excluded population apparently had a relatively concentrated population of those who went on to C-sections.

Dr. Corrado also noted that the statistical outcomes were different if the ACOG definition of metabolic acidosis (pH<7.00 and Bdef>12.0) were used in place of the sponsor definition (pH<7.05), and that use of the ACOG definition affected achievement of statistically significant outcomes. She listed adverse events in each arm. Other FDA issues involving the Swedish RCT were the lack of an automatic ST event signal, deviations from the RCT protocol, retraining of the clinicians during the Swedish RCT, and intercountry differences in clinical practice. There were no FDA biostatistical issues regarding presentation of efficacy data for primary and secondary endpoints.

Dr. Corrado briefly outlined the various studies. The Plymouth RCT of 2434 high- risk labors showed a reduction in ODFD and CSFD in the STAN +FHR arm and a trend toward reduction in metabolic acidosis in the STAN+FHR arm, but found little difference in cases of asphyxia. The EC multicenter trial of 320 evaluable cases was a prospective recruitment, retrospective analysis with blinded ST, in which 11 out of 12 cases with evidence of hypoxia or asphyxia showed ST changes and one case resulting in cerebral palsy had a normal FHR and ST. The Nordic study involved 574 full-term deliveries with unblinded ST data but management based on FHR only. A retrospective evaluation of tracings that was blinded to clinical outcome

found a 100% sensitivity for the STAN guidelines to recommend intervention for cases with neurological symptoms and/or metabolic acidosis. The City of Gothenburg experience with the device over a 16-month period with 2821 labors monitored with the device showed a reduction in cases with metabolic acidosis, moderate/severe encephalopathy, ODFD, and CSFD with experience. There were six cases of moderate/severe encephalopathy and one perinatal death.

Dr. Corrado added that the EU plan for dissemination of knowledge involved regional "hubs of experience/ or centers of excellence for knowledge transfer. After showing further case studies and sample tracings, Dr. Corrado read the questions for panel discussion.

Panel Discussion

Panel Chair Dr. Blanco invited lead panel reviewer Dr. Ramin and other panel members to ask sponsors for clarifications on factual issues. Questions from the panel included the sponsors' definition of midcavity operative delivery and whether there were cultural differences involved in the frequency of that occurrence, whether there were audible or settable alarms, clarification on the lead configuration and placement, and content of original training versus retraining. There was discussion about whether the Gothenburg data were from a clinical trial or from use in general practice and about what those data actually showed. There was panel discourse with sponsors on whether the primary trigger for intervention was information from EFM or information from the ST segment. The panel had considerable discussion on comparability of labor management in Sweden and the United States, with questions on whether physicians were actually in the labor suite throughout the process. Other questions involved the definition of or cutoff for metabolic acidosis and how the management guidelines for intervention were developed.

FDA Questions

Safety and Effectiveness

1a. The primary endpoint for the Swedish trial is metabolic acidosis. Is this endpoint appropriate?

The panel thought metabolic acidosis was a reasonable endpoint but stressed that it is a surrogate for the measurement of neurological damage or injury.

1b. Is the definition of metabolic acidosis (umbilical cord arterial pH <7.05 and base deficit >12mmol/L) clinically meaningful?

The panel discussed this issue extensively, noting their preference for a cutoff of 7.00 because of their greater familiarity with it. The idea of looking at metabolic acidosis as a continuous variable or with an ROC curve was suggested. Sponsors replied that the key issue is avoiding a base deficit of greater than 12, which is associated with a pH of less than 7.05. Some members of the panel thought that the study should be accepted as it was designed, given the reasonableness of its calculations and the lack of a gold standard, but others argued that the definition of metabolic acidosis, as a surrogate endpoint, must be defined appropriately and stringently enough to make this a clinically meaningful cutoff. The panel asked sponsors to analyze the sensitivity and specificity of using the 7.05 cutoff in the 7 reported control cases of encephalopathy.

2. *Please discuss the clinical significance of the results for the primary endpoint (metabolic acidosis) in Analysis I and Analysis II and for the secondary endpoint and other measures (all operative interventions, fetal distress and C-section, fetal distress) in the intent-to–treat group.*

The panel continued to debate whether the proposed definition of metabolic acidosis could help reduce the small but important number of adverse events. There was discussion without

resolution of whether a likelihood ratio was better than trying to measure sensitivity and specificity in a randomized controlled trial and which was more appropriate. The sponsors presented statistics on the reported cases of moderate and severe encephalopathy; their conclusion was that there was no real difference between 7.05 and 7.00 as cutoff points. In terms of the secondary endpoint and other measures, the panel noted U.S. and Swedish differences in the various operative delivery categories and was inclined to lump several data sets under the broad heading of operative delivery, but disagreed on whether the device lowered operative rates for fetal distress. Concern was voiced that in the U.S. obstetrical culture, this device had the potential to increase the C-section rate.

3. *Please discuss the implications of each issue below in relation to the clinical significance of the results presented in Question 2.*

    a. *deviations from the RCT patient management protocol*

Some members of the panel thought that the deviations from protocol were equal in the control and device groups and therefore canceled each other out statistically. Others thought that the number of protocol deviations suggested difficulties in translating the procedure into a practical management regime in the United States.

    b. *no registration of an automatic ST event*

The panel found the sequence of case management and the procedural card very difficult to understand and recommended making it more "Americanized" and user-friendly. They also suggested the addition of an audible ST event alarm.

    c. *Exclusions based on inadequate recordings*

The panel looked at data explaining the number of exclusions for inadequate recordings and concluded that most patients in the device group delivered their babies before the 20- minute period required for obtaining a good reading. They did not see that this presented implications for the clinical significance of the study findings.

d. Inter-country population and management differences

The panel voiced great concern over this issue, citing inter-country differences in how patients are monitored, nurse to patient ratio, and attitudes toward cardiotocography. They noted that the U.S. population is very heterogeneous and were concerned about the false positive rate in a large and diverse population. Concerns were expressed that the device would fail if it were introduced into the United States without extensive education and training and without "Americanization" of the device instructions.

e. Retraining during the Swedish RCT

The panel thought that the Swedish retraining experience underscored the need for education and retraining before the device is introduced to the American market. They recommended that instructions must clearly specify what the device does versus what the practitioner is accustomed to doing. The panel expressed extensive concerns about the need for more labeling, training, certification, and a significant educative process in the U.S. context.

4. *To what extent do results from these studies support the safety and efficacy of the STAN monitor? a) The Plymouth RCT b) The EC Study c) The Nordic Study d) The City of Gothenburg observational study*

The panel thought that the Plymouth study was not designed or powered for the same endpoint as the Swedish study but did show some reduction in the delivery rate for fetal distress. They concluded that the EC and Nordic studies showed a reduction in operative deliveries after

experience in device use. The results from the Gothenburg observational study were less clear-cut, with one member stating that this study showed the value of education in making a difference even in the non-device group.

5. *Do the PMA data support the sponsor's proposed indication for use? Do you have any suggestions for modifications?*

The panel had two issues with the proposed indication for use: they recommended tightening the language to restrict its use for high-risk patients and collection of more information on use with low-risk populations and the number of possible false positives.

6. *Are the professional labeling and the training materials provided by the sponsor sufficient to ensure appropriate use of the STAN system?*

The panel stated that the labeling and training materials provided were not sufficient. They recommended "Americanization" of the materials for the U.S. market and stressed that the educational materials were a key part of this product. The panel recommended that sponsors get input from ACOG on how to prepare the obstetric community for proper device use.

7. *If the panel votes to recommend approval for the STAN monitor, is there a need for postapproval studies? If so, what is the purpose of such studies and what are the key elements of the study design?*

Initial comments from the panel suggested that U.S. postmarketing studies should provide information on the introduction of the technique into U.S. practice and whether it leads to improved clinical outcomes. However, several panel members did not want to address this issue before addressing whether the device should be approved at all.

In clarification of earlier panel questions, sponsors noted that all complaints of technical failures had dealt with printer issues, not questions of safety. They also clarified that best use of the device would be at six to seven centimeters of dilation.

Open Public Hearing

There were no additional requests to address the panel from the audience or from the FDA.

The sponsors commented that the value of the Gothenburg study, which was not randomized, was that it provided the opportunity, along with the clinical trial data, to look at two quite different groups of high and low risk and that it added information on STAN use in a general population.

Panel Deliberations and Vote

Panel Executive Secretary Joyce Whang read the panel the regulatory definitions and panel voting options. **Panel Chair Dr. Blanco** asked if anyone was prepared to make a motion recommending the PMA as approvable with no conditions. No such motion was made. A motion was then made (Dr. Iams) and seconded (Dr. Eglinton) to recommend the PMA as not approvable on the grounds that the device had not demonstrated its efficacy in improving fetal outcome and that the results demonstrated in Sweden might not be replicable in the United States because of differences in obstetric practice. In discussion of the motion, panel members suggested that what was necessary to put the PMA into approvable form would be a study in the United States to show that the results were transportable and that perinatal outcomes could be improved by device use.

Clarification was requested on the difference between a recommendation of not approvable and one of approvable with conditions, with the condition being a study in the United States. **Nancy Brogdon, Director of the Division of Reproductive, Abdominal, and Radiological Devices,** clarified that if the panel required a totally new study before

approving device use in the United States, the motion should be made that the PMA is recommended as not approvable. If the panel thought the device could be on the market and a postmarketing study used to collect U.S. data, then a motion could be made recommending the PMA as approvable with the condition of a postmarket study. **Mr. Pollard** added that the probable benefit must outweigh risks and that the scientific evidence must show a clinically provable result for a PMA to be recommended as approvable.

Industry Representative Mary Lou Mooney pointed out that two randomized controlled clinical trials outside the United States had demonstrated a significant improvement in fetal outcomes with the device and suggested approval for a narrower indication with high-risk patients, along with an extensive training program.

Panel member Robert N. Wolfson spoke in favor of recommending the PMA as approvable. He stated that although he shared the concerns of other panel members about effectiveness in a U.S. population, he thought the device had shown improved neurological outcomes in the United Kingdom and Scandinavia and represented a paradigm shift in showing a correlation of signal analysis to outcome. He saw no evidence that the device causes harm and recommended using the device under a tighter indication rather than delaying its use for years until a trial proves efficacy in a U.S. population.

Other panel members disagreed, stating that the Plymouth study data showed no difference in neurological outcomes and the Gothenburg study showed only greater expertise in reading study traces, which left the Swedish trial, with outcomes they found debatable.

After further discussion, the panel voted to recommend the PMA as not approvable, by a vote of six to five. In post-voting comments, those who voted to recommend the PMA as not

approvable said that they did so because they did not feel the PMA provided reasonable assurance of safety and efficacy. Those who voted against recommending the PMA as not approvable stated that they thought scientific concerns could have been addressed through a more restrictive indication for use and a postmarket study without the time and expense of a U.S. randomized controlled trial. Mr. Pollard asked the panel for clarification on endpoints for a U.S. trial. Panel members suggested metabolic acidosis and clinical markers for newborn encephalopathy and recommended that the U.S. study not be done solely in urban centers.

Adjournment

Panel Chair Dr. Blanco thanked the sponsors, panel, and FDA staff for their work and adjourned the Open Session at 4:00 p.m.

I certify that I attended the Open Session of the Obstetrics and Gynecology Devices Advisory Panel Meeting on April 22, 2002, and that this summary accurately reflects what transpired.

_____

Joyce Whang, Ph.D.
Panel Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

_____

Jorge D. Blanco, M.D.
Panel Chair

Summary minutes prepared by
Aileen M. Moodie
9821 Hollow Glen Pl.
Silver Spring, MD 20910
301-587-9722